Drug Therapy of Bronchial Asthma

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Bronchial Asthma →

Attacks of:

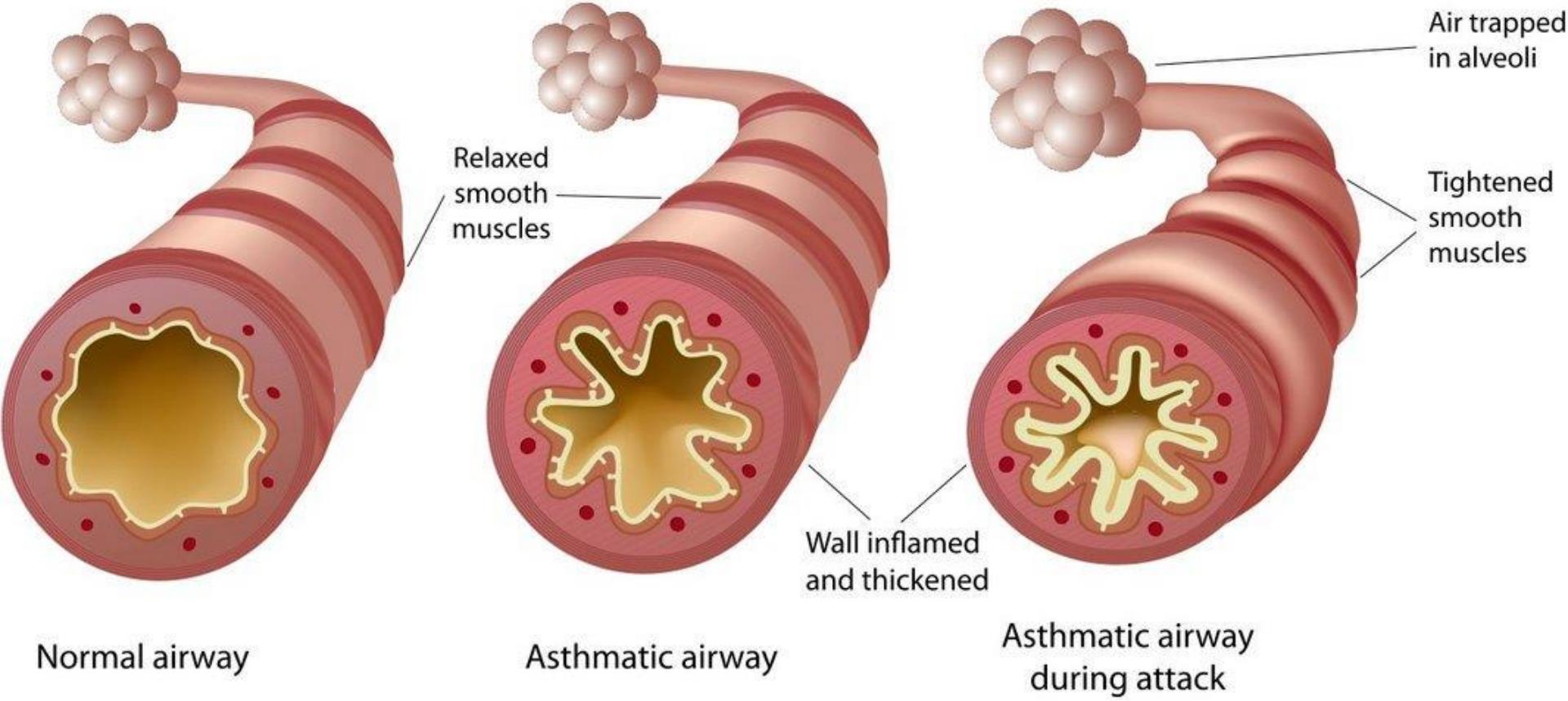
- Chest wheezing
- Shortness of breath
- Cough

Asthma essential features

1. Airways inflammation & obstruction (recurrent, reversible).
2. Bronchial hyper-responsiveness.

Asthma is:

- An inflammatory disease
- A bronchoconstrictive disease

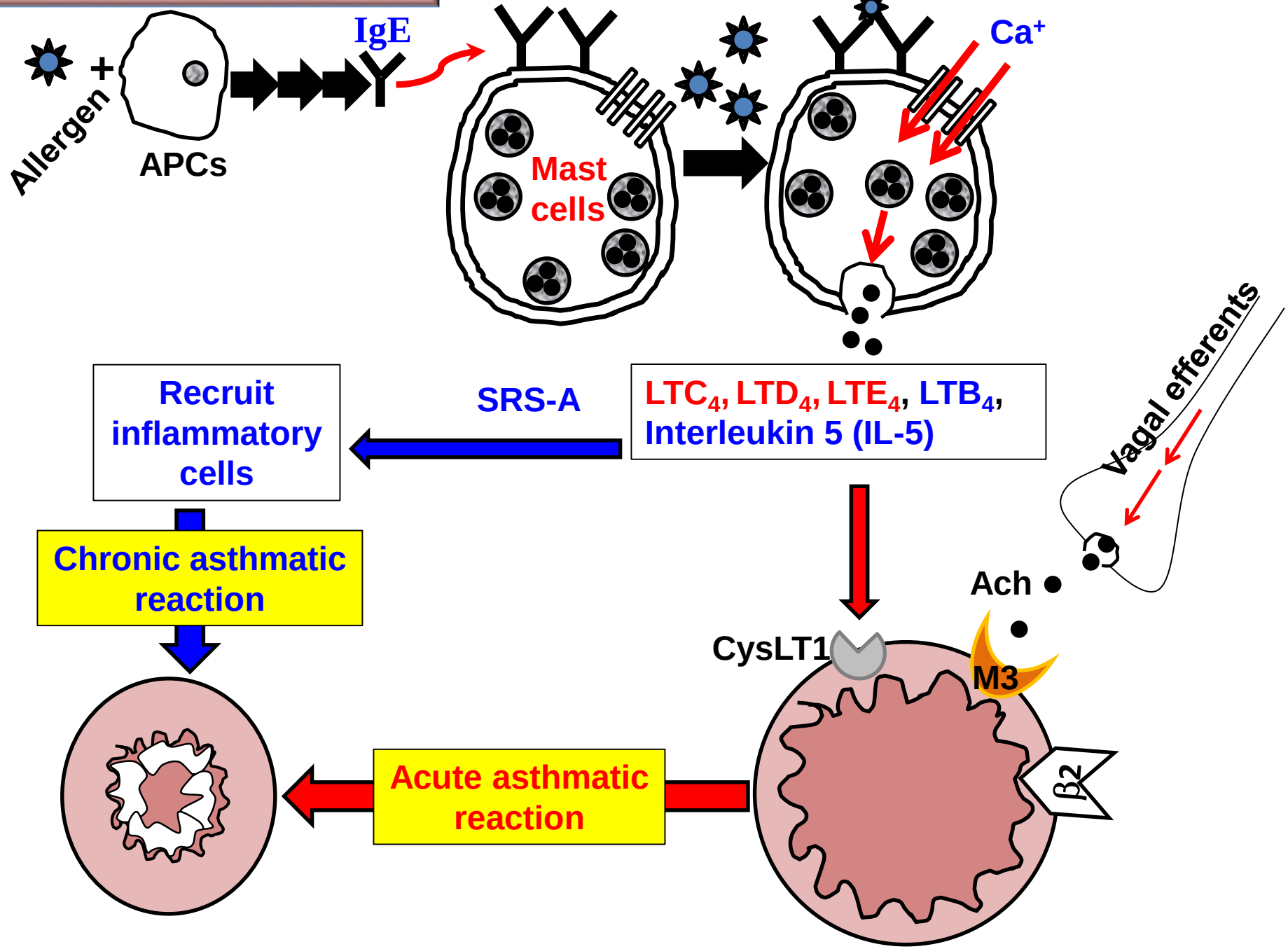

Air trapped
in alveoli
Relaxed
smooth
muscles
Tightened
smooth
muscles
Wall inflamed
and thickened
Normal airway
Asthmatic airway
Asthmatic airway
during attack

Precipitating Factors

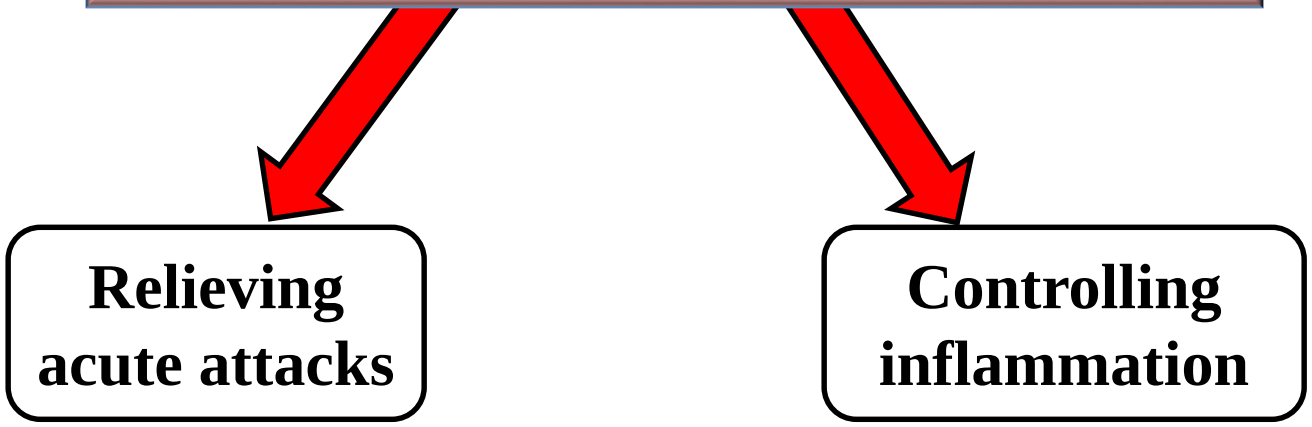
- **Environmental factors**:
  1) Air born particles/pollutants (dust, smoke, pollen grains, etc….)
  2) Cold whether.
- **Drug-induced**
  1) Beta blockers.
  2) NSAIDS.
- **Disease-induced**

  Chest infections.

Asthma pathophysiology



Goals of Asthma Treatment

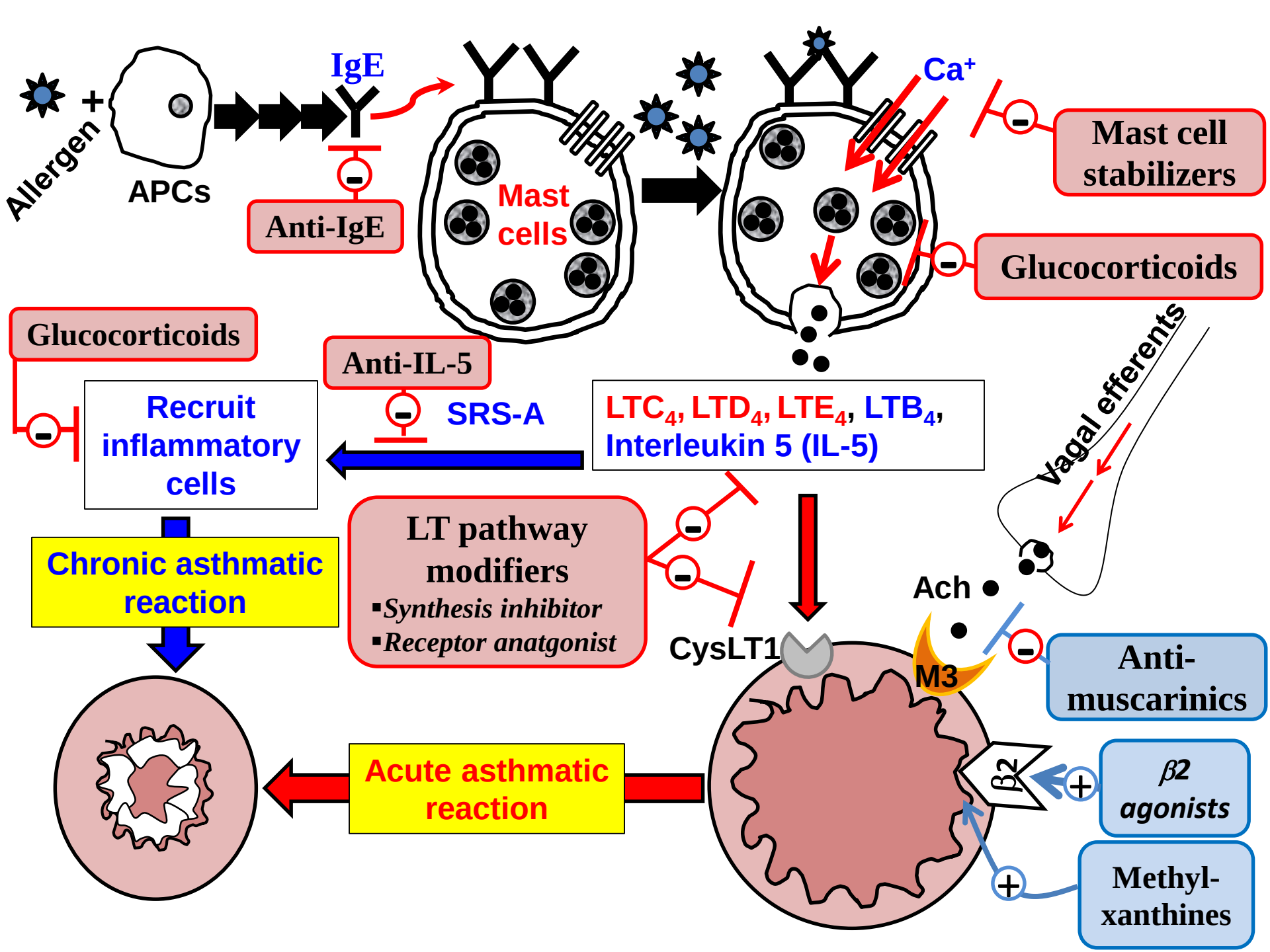


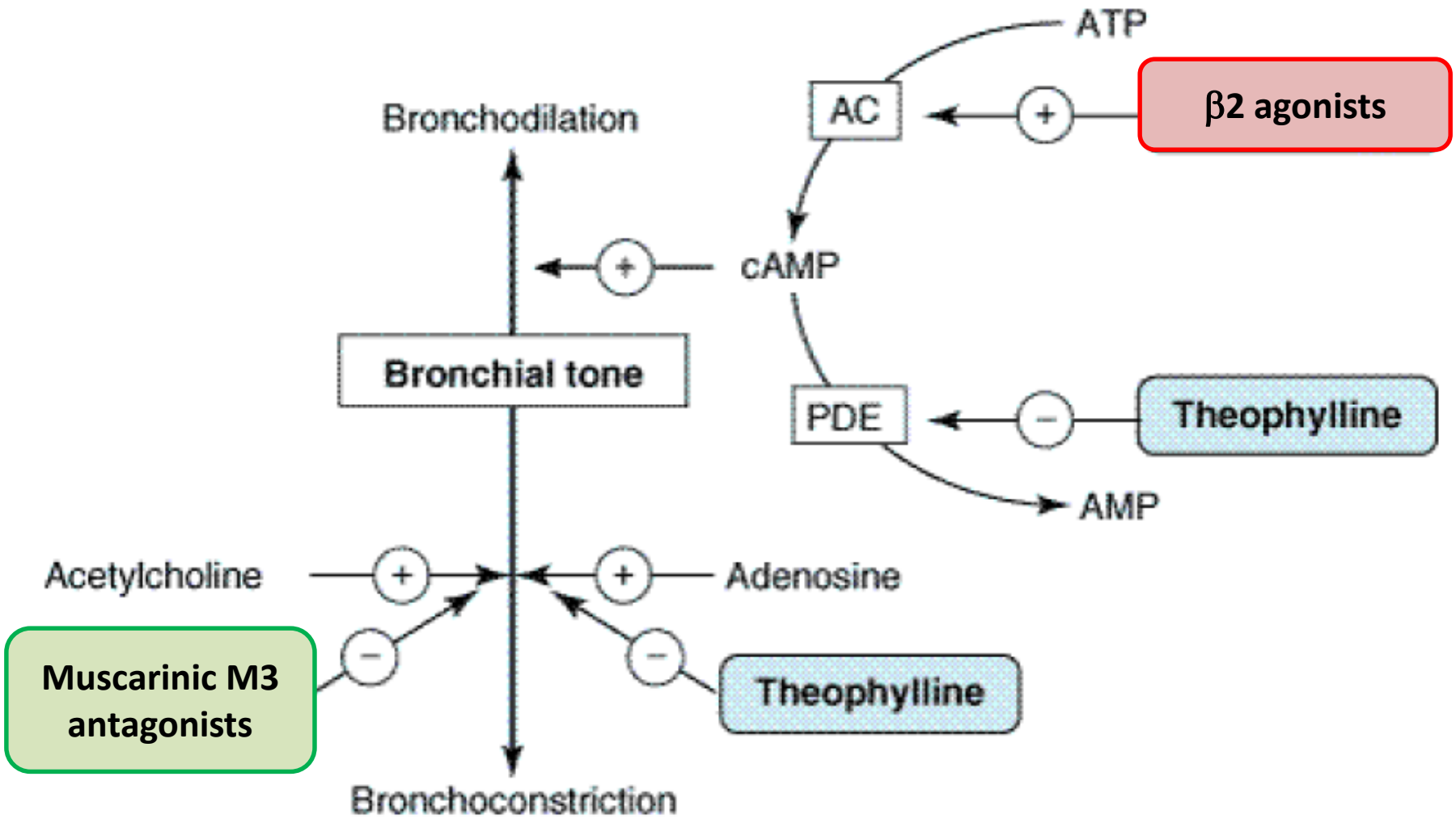
Bronchodilators

1) β_2-adrenergic agonists.
2) Anticholinergic agents (M_3 antagonists).
3) Methylxanthines.

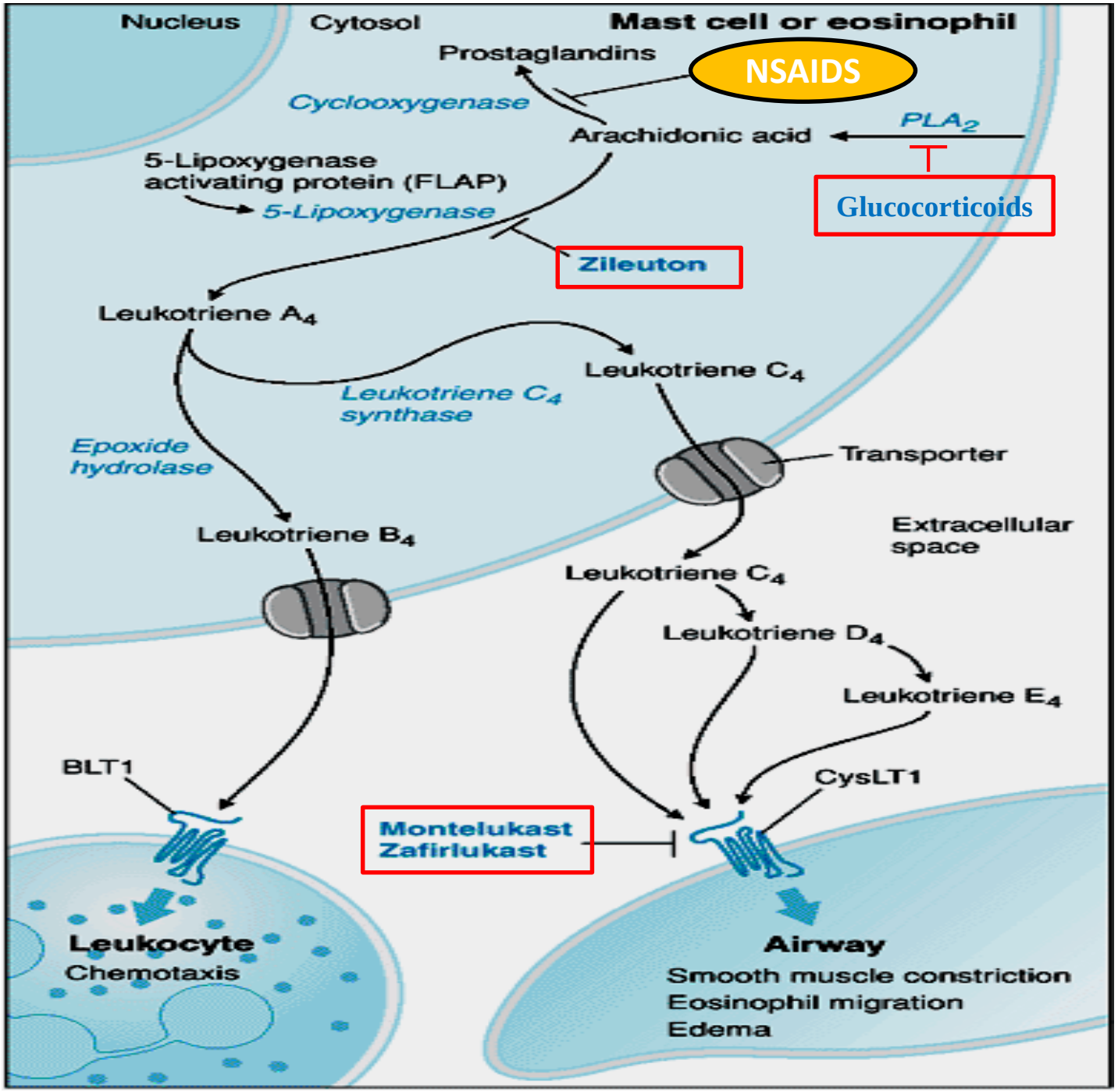
Anti-inflammatory agents

1) Mast cell stabilizers.
2) Leukotriene Pathway-Modifiers:
   - leukotriene synthesis inhibitors.
   - leukotriene receptor antagonists.
3) Glucocorticoids.
4) Anti-IgE or anti-IL5 Antibodies.


Allergen
APCs
IgE
Anti-IgE
Mast cells
Ca+
Mast cell stabilizers
Glucocorticoids
Glucocorticoids
Recruit inflammatory cells
Anti-IL-5
SRS-A
LTC4, LTD4, LTE4, LTB4, Interleukin 5 (IL-5)
Vagal efferents
Chronic asthmatic reaction
LT pathway modifiers
▪Synthesis inhibitor
▪Receptor anatgonist
CysLT1
Ach
M3
Anti-muscarinics
β2
β2 agonists
Methyl-xanthines
Acute asthmatic reaction


ATP
AC
β2 agonists
Bronchodilation
cAMP
Bronchial tone
PDE
Theophylline
AMP
Acetylcholine
Adenosine
Muscarinic M3 antagonists
Theophylline
Bronchoconstriction

Treatment of **Acute attacks**	**β_2-adrenoceptor agonists** ***e.g.,*** ***Short acting:*** *[Salbutamol (albuterol) levalbuterol , terbutaline]* ***Long acting:*** *[Salmeterol Formoterol]*	**Anticholinergic agents** ***e.g.,*** *Ipratropium Tiotropium (slow dissociation from M3 receptors → longer duration)*	**Methylxanthines** ***e.g.,*** *Theophylline Aminophylline*
M.O.A	Θ airway smooth muscles contraction via: 1) ↓ myosin light chain kinase activity 2) Open calcium-activated potassium channels (K_{Ca}) → hyperpolarization	ΘAch at muscarinic M_3 receptors→ ▪↓ smooth muscle contraction (*slow onset??)* ▪ ↓**mucus hypersecretion**	Θ airway smooth muscles contrac.via: ▪Θphosphodiester-ases, (isoform 4) (PDE4)→↑cAMP ▪Comp. antag. @adenosine receptors
Indic.	Rapid relief of acute asthmatic attacks	< effective than β_2-agonists ▪Intolerance to inhaled β_2-agonists. ▪In combination with β_2-adrenoceptor agonists	Similar to β_2-agonists (*but with narrow therapeutic window)*
S.E.	Systemic absorption→ ▪tremor ▪tachycardia ▪arrhythmia	Powder→ ▪throat irritation ▪cough	▪arrhythmia ▪ nausea & vomiting


Nucleus
Cytosol
Mast cell or eosinophil
Prostaglandins
NSAIDS
Cyclooxygenase
Arachidonic acid
PLA2
5-Lipoxygenase activating protein (FLAP)
5-Lipoxygenase
Glucocorticoids
Zileuton
Leukotriene A4
Leukotriene C4
Leukotriene C4 synthase
Epoxide hydrolase
Transporter
Leukotriene B4
Extracellular space
Leukotriene C4
Leukotriene D4
Leukotriene E4
BLT1
CysLT1
Montelukast
Zafirlukast
Leukocyte
Chemotaxis
Airway
Smooth muscle constriction
Eosinophil migration
Edema

	Leukotriene Pathway Modifiers ***e.g.,*** ▪*Zileuton* ▪*Motelukast, Zafirlukast , Pranlukast*	**Glucocorticoids** ▪**Inhaled** *(e.g., fluticasone and budesonide)* ▪**Systemic** *(e.g., prednisone*)	**Mast cell stabilizers** *e.g., cromolyn sodium, nedocromil sodium, ketotifen*
M.O.A	***Zileuton****:* Θ 5-lipoxygenase (5-LOX) → Θ leukotriene synthesis ***Lukasts***: Comp. antag. of cysteinyl leukotriene receptor CysLT1	Θ phospholipase A2 (PLA2)→↓synthesis of AA-derived inflamm. mediators	*Indirect* inhibition of calcium influx→ Θ degranulation
Indic.	**Long-term control**		
	Pharmacogenetic variability!!	***Systemic*** (I.V.) → Severe asthma attacks	
S.E.		***Inhaled*** → Orophar. candidiasis & dysphonia ***Systemic*** → brief TTT course (5-10 days) → impair glucose control	***Inhaled***:→ throat irritation, cough, & mouth dryness. ***Ketotifen*** → headache & H_1-*antagonists-like SE*

	Anti-IgE Monoclonal Antibodies ***e.g.,*** *Omalizumab* *(given by S.C.)*	**Anti-IL-5 Monoclonal Antibodies** ***e.g.,*** *Mepolizumab (given by S.C. or I.V.)* *Reslizumab* *(given by I.V.)*
M.O.A	Neutralization of IgE→ Θbinding of IgE to **mast** cells→ Θdegranulation	Neutralization of IL-5 which is responsible for the survival, differentiation, recruitment, and activation of **eosinophils**→ Θdegranulation
Indic.	**Long-term control**	
	Severe uncontrolled allergic asthma (in atopic patients) (eosinophils >150 cells/microL) (age > 12 yeas old for omaliumab & mepozumab; while >18 years old for reslizumab)	
S.E.	**Most common**: headache, injection site inflamm. reactions (S.C.) , back pain, and fatigue. **Less frequently** Hypersensitivity reactions (e.g., angioedema, bronchospasm, hypotension, urticaria, rash)	